

Title: Oral-Facial-Digital Syndrome Type 1 *GeneReview* – Table 1

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Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

Table 1. OFD Syndromes: Clinical Features and Causal Genes

	Oral Features	Facial Features	Hand Anomalies	Foot Anomalies	Skin/Hair Features	Renal Features	Cardiac Features	Cerebral Features	Skeletal Features	Other Abnormalities	Inheritance
OFD I	Gingival frenulae Lingual hamartomas Cleft/lobulated tongue Cleft palate	Hypertelorism Cleft lip Pseudocleft of the upper lip	Brachydactyly Clinodactyly Polydactyly	Preaxial polydactyly	Milia Alopecia	Polycystic kidney disease	-	Corpus callosum agenesis Cerebellar hypoplasia	-	Moderate intellectual disability (50%)	X-linked dominant (lethal in males)
OFD II	Gingival frenulae Lingual hamartomas Cleft/lobulated tongue Cleft palate	-	Brachydactyly Clinodactyly Polydactyly	Broad hallux Pre/postaxial polydactyly	Thick hair	-	Rare	Porencephaly Hydrocephaly	Median Y-shaped metacarpal	-	Autosomal recessive
OFD III	Bifid uvula Lingual hamartomas Lobulated tongue Tooth hypoplasia	Hypertelorism Bulbous nose Low-set ears	Postaxial polydactyly	Postaxial polydactyly	-	End-stage renal failure at 13 and 24 years old	-	Cerebellar vermis hypoplasia DW malformation with cystic dilation of the fourth ventricle Myoclonia / eye movement	-	Pectus excavatum Severe intellectual disability	Autosomal recessive
OFD IV	Gingival frenulae Lingual hamartomas Lobulated tongue Cleft palate	Epicanthus Micrognathia Low-set ears	Brachydactyly Clinodactyly Pre/postaxial polydactyly	Pre/postaxial polydactyly	-	Renal cysts	-	Porencephaly Occipital encephalocele Agenesis of corpus callosum Cerebellar vermis hypoplasia w/MTS	Pectus excavatum Tibial abnormalities	Short stature Variable intellectual disability	Autosomal recessive

OFD V	Gingival frenulae (rare)	Midline cleft lip	Postaxial polydactyly	Postaxial polydactyly	-	-	-	-	-	India origin	Autosomal recessive
OFD VI	Gingival frenulae Lingual hamartomas Lobulated tongue Cleft palate	Hypertelorism Cleft lip	Brachydactyly Clinodactyly Syndactyly Median/postaxial polydactyly	Broad hallux Preaxial polydactyly	-	Renal agenesis Renal dysplasia	Rare	Cerebellar vermis hypoplasia with MTS	Median Y-shaped metacarpal	Variable intellectual disability Possible retinopathy	Autosomal recessive
OFD VII	Gingival frenulae Lingual hamartomas Cleft palate	Hypertelorism Cleft lip Asymmetry	Clinodactyly	-	-	Polycystic kidney disease	-	-	-	Moderate intellectual disability	X-linked dominant
OFD VIII	Gingival frenulae Lingual hamartomas Lobulated tongue Epiglottis hypoplasia	Midline cleft lip Telecanthus Large nose	Bifid thumb Postaxial polydactyly	Preaxial polydactyly	-	-	-	-	Tibia and radius hypoplasia	Psychomotor delay Precocious lethality	X-linked recessive
OFD IX	Gingival frenulae Lingual hamartomas Lobulated tongue Cleft palate	Midline cleft lip Synophrys	Brachydactyly Clinodactyly Polydactyly	Bifid toes	-	-	SD	-	-	Short stature Microphthalmia Coloboma	Autosomal recessive

OFD X	Gingival frenulae Cleft palate	Telecanthus Flat nasal root Retrognathia	Oligodactyly Preaxial polydactyly	-	-	-	-	-	Shortened 4 limbs Bilateral short radii Fibular agenesis	-	Sporadic
OFD XI	Gingival frenulae Cleft palate	Hypertelorism Auricular pits Blepharophimosis	Postaxial polydactyly	Postaxial polydactyly	-	-	-	Ventricular dilatation	Odontoid hypoplasia Vertebral abnormalities	Deafness Severe intellectual disability Behavioral abnormalities	Sporadic
OFD XII	Gingival frenulae Bifid tongue Supernumerary teeth	Macrocephaly Hypertelorism	Pre/postaxial polydactyly	Preaxial polydactyly Club feet	-	-	Septum hypertrophy	Aqueductal stenosis Corpus callosum agenesis Cerebellar vermis hypoplasia Myelomeningocele	Short tibiae Central Y-shaped metacarpal	-	Sporadic
OFD XIII	Lingual hamartomas	Cleft lip	Brachydactyly Clinodactyly Syndactyly	Brachydactyly Clinodactyly Syndactyly	-	-	Mitral and tricuspid valves dysplasia	Leukoaraiosis	-	Neuropsychiatric disease Epilepsy	Sporadic
OFD XIV	Gingival frenulae Lingual hamartomas Cleft/lobulated tongue Cleft palate	Telecanthus	Postaxial polydactyly	Duplication of hallux	-	-	-	Corpus callosum agenesis Cerebellar vermis hypoplasia with MTS	-	Severe microcephaly Micropenis	Autosomal recessive
Unclassified OFD	Lobulated tongue Cleft palate	Median cleft lip	Postaxial polydactyly	NA	Thick hair	Fused kidneys	TOF VSD	Corpus callosum agenesis		Possible moderate intellectual disability Hirschsprung disease	Autosomal recessive
Unclassified OFD	Lingual hamartomas	Frontal bossing	Postaxial polydactyly	Duplication of hallux	-	-	Coarctation of the aorta	-	5 th Y-shaped metacarpal	+/- intellectual disability	Autosomal recessive

		Hypertelorism Micro-retrognathia		Syndactyly							
Unclassified OFD	Lingual hamartoma	Frontal bossing Cleft lip Low-set ears Micro-retrognathia	Preaxial polydactyly	Polydactyly	-	-	TOF	NA	Y-shaped metatarsal	Intellectual disability, micropenis	Autosomal recessive
Unclassified OFD	Cleft palate	Cleft lip	Postaxial polydactyly	Postaxial polydactyly	-	-	-	Cerebellar vermis hypoplasia, DW malformation	12 th rib hypoplasia	-	Autosomal recessive
Unclassified OFD	Gingival frenulae	Cleft lip	Brachydactyly Preaxial polydactyly	Postaxial polydactyly	-	-	-	-	Short stature Short mesoaxial phalanges	-	Autosomal recessive

DW = Dandy-Walker; MTS = molar tooth sign; SD = septal defects; TOF = tetralogy of Fallot; VSD = ventricular septal defect

Characteristic features for each subtype are in **bold**.

References

Chevrier V, Bruel A-L, van Dam TJP, Franco B, Scalzo ML, Lembo F, Audebert S, Baudelet E, Isnardon D, Bole A, et al. OFIP/KIAA0753 forms a complex with OFD1 and FOR20 at pericentriolar satellites and centrosomes and is mutated in one individual with oral-facial-digital syndrome. *Hum Mol Genet* 2016;25:497-513.

Darmency-Stamboul V, Burglen L, Lopez E, Mejean N, Dean J, Franco B, Rodriguez D, Lacombe D, Desguerres I, Cormier-Daire V, et al. Detailed clinical, genetic and neuroimaging characterization of OFD VI syndrome. *Eur J Med Genet* 2013;56:301-8.

Degner D, Bleich S, Riegel A, Rütter E. [Orofaciodigital syndrome--a new variant? Psychiatric, neurologic and neuroradiological findings]. *Fortschr Neurol Psychiatr* 1999;67:525-8.

Edwards M, Mulcahy D, Turner G. X-linked recessive inheritance of an orofacioidigital syndrome with partial expression in females and survival of affected males. *Clin Genet* 1988;34:325-32.

Erickson RP, Bodensteiner JB. Oro-facial-digital syndrome IX with severe microcephaly: a new variant in a genetically isolated population. *Am J Med Genet A* 2007;143A:3309-13.

Figuera LE, Rivas F, Cantú JM. Oral-facial-digital syndrome with fibular aplasia: a new variant. *Clin Genet* 1993;44:190-2.

Gabrielli O, Ficcadenti A, Fabrizzi G, Perri P, Mercuri A, Coppa GV, Giorgi P. Child with oral, facial, digital, and skeletal anomalies and psychomotor delay: a new OFDS form? *Am J Med Genet* 1994;53:290-3.

Gurrieri F, Sammito V, Ricci B, Iossa M, Bellussi A, Neri G. Possible new type of oral-facial-digital syndrome with retinal abnormalities: OFDS type (VIII). *Am J Med Genet* 1992;42:789-92.

Lambacher NJ, Bruel A-L, van Dam TJP, Szymańska K, Slaats GG, Kuhns S, McManus GJ, Kennedy JE, Gaff K, Wu KM, et al. TMEM107 recruits ciliopathy proteins to subdomains of the ciliary transition zone and causes Joubert syndrome. *Nat Cell Biol* 2016;18:122-31

Li C, Jensen VL, Park K, Kennedy J, Garcia-Gonzalo FR, Romani M, De Mori R, Bruel A-L, Gaillard D, Doray B, et al. MKS5 and CEP290 dependent assembly pathway of the ciliary transition zone. *PLoS Biol.* 2016;14:e1002416.

Lopez E, Thauvin-Robinet C, Reversade B, Khartoufi NE, Devisme L, Holder M, Ansart-Franquet H, Avila M, Lacombe D, Kleinfinger P, et al. C5orf42 is the major gene responsible for OFD syndrome type VI. *Hum Genet* 2014;133:367-7.

Morán-Barroso V, Valdés Flores M, García-Cavazos R, Kofman-Alfaro S, Saavedra-Ontiveros D. Oral-facial-digital (OFD) syndrome with associated features: a new syndrome or genetic heterogeneity and variability? *Clin Dysmorphol* 1998;7:55-7.

Nowaczyk MJM, Zeesman S, Whelan DT, Wright V, Feather SA. Oral-facial-digital syndrome VII is oral-facial-digital syndrome I: a clarification. *Am J Med Genet A* 2003;123A:179-2.

Obregón MG, Barreiro CZ. Oral-facial-digital syndrome gabrielli type: second report. *Am J Med Genet A* 2003;118A:369-71.

Poretti A, Brehmer U, Scheer I, Bernet V, Boltshauser E. Prenatal and neonatal MR imaging findings in oral-facial-digital syndrome type VI. *AJNR Am J Neuroradiol* 2008;29:1090-1.

Prattichizzo C, Macca M, Novelli V, Giorgio G, Barra A, Franco B. Mutational spectrum of the oral-facial-digital type I syndrome: a study on a large collection of patients. *Hum Mutat* 2008;29:1237-46.

Prpić I, Cekada S, Franulović J. Mohr syndrome (oro-facial-digital syndrome II)--a familial case with different phenotypic findings. *Clin Genet* 1995;48:304-7.

Roberson EC, Dowdle WE, Ozanturk A, Garcia-Gonzalo FR, Li C, Halbritter J, Elkhartoufi N, Porath JD, Cope H, Ashley-Koch A, et al. TMEM231, mutated in orofacioidigital and Meckel syndromes, organizes the ciliary transition zone. *J Cell Biol* 2015;209:129-42.

Saari J, Lovell MA, Yu H-C, Bellus GA. Compound heterozygosity for a frame shift mutation and a likely pathogenic sequence variant in the planar cell polarity-ciliogenesis gene WDPCP in a girl with polysyndactyly, coarctation of the aorta, and tongue hamartomas. *Am J Med Genet A* 2015;167:421-7.

Shamseldin HE, Rajab A, Alhashem A, Shaheen R, Al-Shidi T, Alamro R, Al Harassi S, Alkuraya FS. Mutations in DDX59 implicate RNA helicase in the pathogenesis of orofacioidigital syndrome. *Am J Hum Genet* 2013;93:555-60.

Smith RA, Gardner-Medwin D. Orofaciodigital syndrome type III in two sibs. *J Med Genet* 1993;30:870-2.

Sugarman GI, Katakia M, Menkes J. See-saw winking in a familial oral-facial-digital syndrome. *Clin Genet.* 1971;2:248-54.

Thauvin-Robinet C, Cossee M, Cormier-Daire V, Van Maldergem L, Toutain A, Alembik Y, Bieth E, Layet V, Parent P, David A, Goldenberg A, Mortier G, Heron D, Sagot P, Bouvier AM, Huet F, Cusin V, Donzel A, Devys D, Teyssier JR, Faivre L. Clinical, molecular, and genotype-phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: a French and Belgian collaborative study. *J Med Genet* 2006;43:54-61

Thauvin-Robinet C, Lee JS, Lopez E, Herranz-Pérez V, Shida T, Franco B, Jegou L, Ye F, Pasquier L, Loget P, et al. The oral-facial-digital syndrome gene C2CD3 encodes a positive regulator of centriole elongation. *Nat Genet* 2014;46:905-11.

Thevenon J, Duplomb L, Phadke S, Eguether T, Saunier A, Avila M, Carmignac V, Bruel A-L, St-Onge J, Duffourd Y, et al. Autosomal Recessive IFT57 hypomorphic mutation cause ciliary transport defect in unclassified oral-facial-digital syndrome with short stature and brachymesophalangia. *Clin Genet.* In press.

Thomas S, Legendre M, Saunier S, Bessières B, Alby C, Bonnière M, Toutain A, Loeuillet L, Szymanska K, Jossic F, et al. TCTN3 mutations cause Mohr-Majewski syndrome. *Am J Hum Genet* 2012;91:372–378.

Toriello HV. Oral-facial-digital syndromes, 1992. *Clin Dysmorphol* 1993;2:95-105.

Toriello HV, Carey JC, Suslak E, Desposito FR, Leonard B, Lipson M, Friedman BD, Hoyme HE. Six patients with oral-facial-digital syndrome IV: the case for heterogeneity. *Am J Med Genet* 1997;69:250-60.

Toriyama M, Lee C, Taylor SP, Duran I, Cohn DH, Bruel A-L, Tabler JM, Drew K, Kelly MR, Kim S, et al. The ciliopathy-associated CPLANE proteins direct basal body recruitment of intraflagellar transport machinery. *Nat Genet* 2016;48:648-56

Valiathan A, Sivakumar A, Marianayagam D, Valiathan M, Satyamoorthy K. Thurston syndrome: report of a new case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101:757-60.

Whelan DT, Feldman W, Dost I. The oro-facial-digital syndrome. *Clin Genet* 1975;8:205-12.